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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/551,292	09/28/2005	Isabel Rego Santos	1660 WO/US	1556
7590		12/21/2007	EXAMINER	
Jeffrey S Boone			SCHLIENTZ, LEAH H	
Mallinckrodt Inc				
675 McDonnell Boulevard			ART UNIT	
PO Box 5840			PAPER NUMBER	
St Louis, MO 63134			1618	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/551,292

Applicant(s)

SANTOS ET AL.

Examiner

Leah Schlientz

Art Unit

1618

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 15 October 2007.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-26 and 36-43 is/are pending in the application.
- 4a) Of the above claim(s) 4,5,8-11,13-26,37,39 and 40 is/are withdrawn from consideration.
- 5) ☒ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-3,6,7,12, 36, 38 and 41-43 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 28 September 2005 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
- 1) ☒ Certified copies of the priority documents have been received.
 - 2) ☐ Certified copies of the priority documents have been received in Application No. _____.
 - 3) ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Acknowledgement of Receipt

Applicant's Response, filed 10/15/2007, in reply to the Office Action mailed 6/13/2007, is acknowledged and has been entered. Claims 1, 20 – 23 and 36 – 40 have been amended. New claims 41 – 43 have been added. Claims 1 – 26 and 36 – 43 are pending, of which claims 4, 5, 8 - 11, 13 - 26, 37, 39 and 40 are withdrawn from consideration at this time as being drawn to a non-elected invention. Claims 1 – 3, 6, 7, 12, 36, 38 and 41 – 43 are readable upon the elected invention and are examined herein on the merits for patentability.

Response to Arguments

Applicant's arguments, with respect to the rejection of claims 1 – 3, 6, 7, 12 and 36 under 35 USC 102(b) as being anticipated by Merkle *et al.* (US 5,569,769) have been fully considered and are persuasive. Therefore, the rejection has been WITHDRAWN.

Allowable Subject Matter

Claims 1 – 3, 6, 7, 12, 36, 38 and 41 - 43 are free of the prior art to the extent that they read upon the elected species. However, in accordance with Markush practice, the search was expanded to cover additional non-elected species within the

scope of the pending claims. Grounds for rejection over non-elected species are discussed below.

New Grounds for Rejection

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

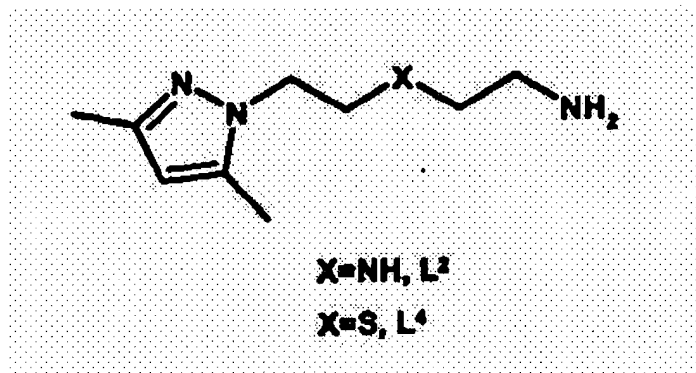
(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1 – 3, 6, 7, 12 and 41 – 43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Alves *et al.* (*J. Chem. Soc. Dalton Trans.*, 2002, p. 4714 – 4719), in view of Hawthorne (US 5,066,479).

Alves discloses the rhenium and ^{99m}technetium coordination capabilities of pyrazolyl containing ligands, such as pz*(CH₂)₂NH(CH₂)₂NH₂ (L²) and pz*(CH₂)₂S(CH₂)₂NH₂ (L⁴), where (pz* = 3,5 Me₂Pz), as shown below.

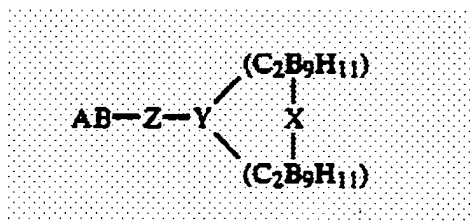


Such compounds are useful in the development of receptor-specific targeting molecules for use in nuclear medicine. The ligands presented in the study of Alves were presented as a part of research to access a general labeling protocol for biomolecules, namely peptides (page 4714, left column). The ligands are shown to present a range of features, namely stability, solubility, coordination possibilities and easy functionalization through the pyrazolyl, the amine groups and the methylenic backbone, which make them promising for biomedical applications, specifically for labeling peptides with the *fac*-[M(CO)₃]⁺ moiety (page 4714, right column).

Accordingly, Alves discloses compounds meeting the formula as claimed in claim 1, but teaches a hydrogen at position R2, rather than a carboxylate or amine functional group. Alves teaches that the ligands may be derivatized to carry a biomolecule (i.e. via functionalization at the pyrazolyl ring). Alves does not specifically teach that such functionalization of the pyrazolyl ring is achieved via a carboxylate or amine group.

However, derivatization of a pyrazolyl ring via a carboxylate or amine functional group is well-known in the art to be a method by which ^{99m}Tc chelating moieties may be

conjugated to a biomolecule. For example, Hawthorne teaches compounds of the following formula:



wherein the carborane moieties chelate a metal or radioisotope X, Y is a pyrazolyl ring, Z is a short chain carbon moiety typically used in linking antibodies to various molecules including carboxyl or amino groups, and AB is an antibody. See Figure 1 and column 3 - 4.

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to derivatize the pyrazolyl ring of the ligands taught by Alves to carry a biomolecule because Alves teaches that said ligands are intended for the stabilization of the $[M(CO)_3]^+$ core and for linking to biomolecules, and one would have been motivated to do so because Alves specifically teaches that said ligands offer easy functionalization through the pyrazolyl ring (see Alves page 1474). Although Alves does teach that such functionalization occurs via a carboxylate or amine group, it would have been obvious to one of ordinary skill in the art to utilize such groups because Hawthorne teaches that carboxyl and amino groups on a short chain carbon moiety are the groups which are typically used to link a biomolecule, such as an antibody, to a radionuclide chelating moiety (i.e. including through conjugation to position R2 of a pyrazolyl ring). One would have expected a reasonable degree of success in doing so because Hawthorne teaches that the use of such linking moieties is well-known and has been conventionally

used in conjugating antibodies to a wide variety of molecules (see Hawthorne Figure 1 and column 4, lines 5 – 10).

Claims 36 and 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Alves *et al.* (*J. Chem. Soc. Dalton Trans.*, 2002, p. 4714 – 4719), in view of Merkle *et al.* (US 5,569,769).

Alves discloses the rhenium and ^{99m}technetium coordination capabilities of pyrazolyl containing ligands, such as pz*(CH₂)₂NH(CH₂)₂NH₂ (L²) and pz*(CH₂)₂S(CH₂)₂NH₂ (L⁴), where (pz* = 3,5 Me₂Pz) for use in nuclear medicine, as set forth above.

Accordingly, Alves discloses compounds meeting the formula as claimed in claims 1, 36 and 38, but teaches methyl substituents at positions R1 and R3, rather than a phenyl or aryl, as claimed.

Merkle teaches pyrazole derivatives of general formula I, in which at least one of radicals R¹-R⁴ is not hydrogen and their use in preparing pharmacologically active compounds. Suitable substituents on the pyrazole ring positions include C₁-C₁₀ alkyl, aryl groups, such as phenyl, etc. (column 3).

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to provide a compound having a phenyl substituent, rather than methyl substituents, at position R1 and/or R3 of the ligands disclosed by Alves. One of ordinary skill in the art would have had a reasonable expectation of success in doing so because such substituents (i.e. methyl and phenyl) are shown in the art to be equivalent

substituents used in derivatization of a pyrazole ring, e.g. for use in preparing pharmacologically active compounds, as shown by Merkle. One of ordinary skill would have had a reasonable expectation of success in such substitutions providing properties such as altered solubility, steric qualities, etc.

Conclusion

No claims are allowed at this time.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leah Schlientz whose telephone number is 571-272-9928. The examiner can normally be reached on Monday - Friday 8 AM - 5 PM.


If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Hartley can be reached on 571-272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business

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Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

LHS



MICHAEL G. HARTLEY
SUPERVISORY PATENT EXAMINER